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Palladium-Catalyzed Synthesis of α-Iminonitriles from Aryl Halides via Isocyanide Double Insertion Reaction

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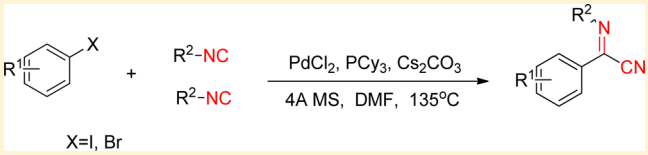
Supporting Information

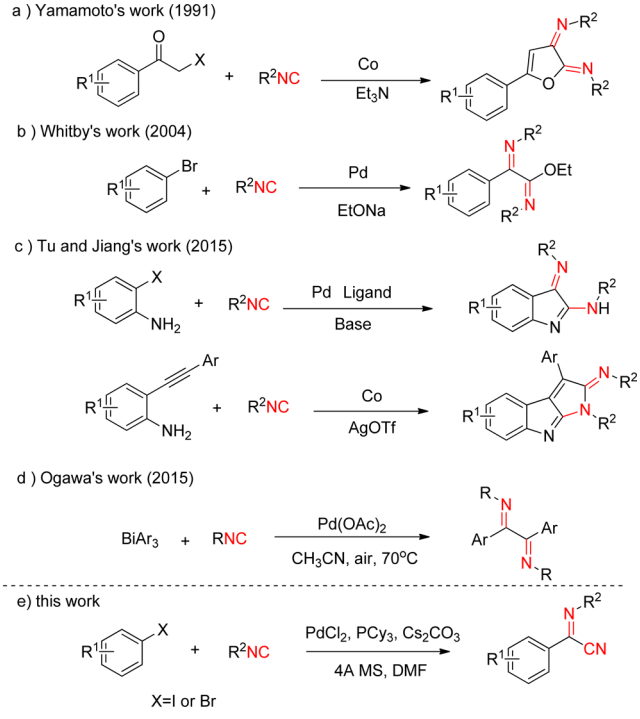
ABSTRACT: An efficient one-pot synthesis of α-iminonitriles from readily available aryl halides via palladium-catalyzed double isocyanide insertion and elimination has been developed, without using various hypertoxic cyanides and excess oxidants. Furthermore, the utility of this reaction was demonstrated by the rapid total synthesis of quinoxaline and the reaction of functional groups exchanged with aryl halides.



INTRODUCTION

Isocyanides are an important class of organic molecules which have been widely applied in organic, medicinal, and combinatorial chemistry since the Passerini and Ugi reactions were discovered.[1] In the past decade, isocyanides have emerged as versatile C_1 building blocks to build C−C,[2] C−N,[3,4] and C−O[5] bonds in palladium-catalyzed two-component reactions and evolutionary multicomponent reactions (MCRs). Recently, *tert*-butyl isocyanide as a cyanide alternative has been reported,[6] which further broadened the application of isocyanides in organic synthesis. During the past few years, our group has synthesized many kinds of organic compounds including isocoumarins, phthalides,[5c] quinazolinones,[3e] diazoles,[4c] indenoindolones,[2h] alkynones,[2c] indane-1,3-dione,[2f] diarylketones,[2g] and aryl aldehydes[7] via palladium-catalyzed isocyanide insertion into C−X bonds (X = Br, I). Nevertheless, the most reported achievements mainly focus on the utility of isocyanides single insertion for the synthesis of nitrogen-containing compounds. Readily polymerized in the presence of a transition metal,[8] isocyanides were seldomly used for multiple insertion reaction, especially for the reaction of isocyanide multiple insertion at the same site. Only a few examples of metal-catalyzed double isocyanides insertion have been reported. For instance, in 1991, Yamamoto and co-workers[9] reported double insertion of isocyanides into a metal−carbon bond through cobalt-catalyzed (Scheme 1a). In 2004, Whitby et al.[10] reported palladium-catalyzed double isocyanide insertion into aryl bromides for the synthesis of α-iminoimidates (Scheme 1b). Recently, Tu and Jiang developed a palladium-catalyzed[3c] or cobalt(II)/silver relay catalyzed[11] isocyanide double insertion intramolecular cyclization for the formation of indole derivatives (Scheme 1c). Subsequently, Ogawa and co-workers[12] achieved isocyanide double insertion into a Pd−C bond for the synthesis of α-diimines (Scheme 1d). Obviously, with the powerful development space and potential application, transition-metal-catalyzed isocyanide multiple insertion reactions have increasingly attracted the attention of a growing number of chemists.

Scheme 1. Metal-Catalyzed Isocyanide Double Insertion Reaction



The α-iminonitriles (imidoyl cyanides) are a valuable class of synthetic intermediates,[13] which could not only serve as precursors for α-ketoacids, amides, *N*-alkylketene−imines,

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Scheme 2. Application of α-Iminonitrile

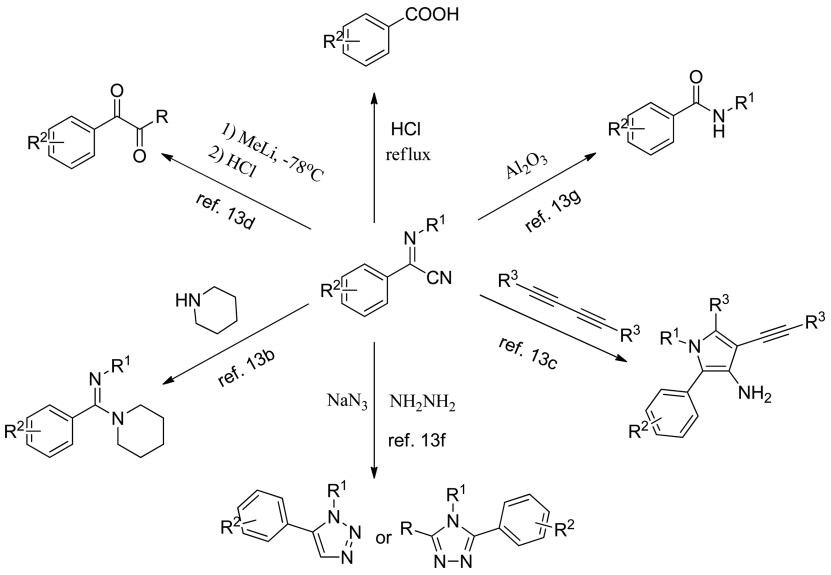
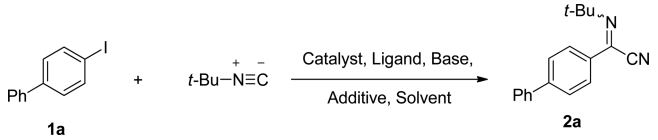


Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	base	additive	solvent	yield [%][b]
1	$Pd(OAc)_2$	PCy_3	K_2CO_3	–	DMSO	31[c]
2	$Pd(OAc)_2$	PCy_3	K_2CO_3	–	DMSO	44[d]
3	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	57[e]
4	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	41[f]
5	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMSO	65
6	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	dioxane	19
7	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	toluene	22
8	$Pd(OAc)_2$	PCy_3	K_2CO_3	4A MS	DMF	61
9	$Pd(OAc)_2$	PCy_3	NaOAc	4A MS	DMF	trace
10	$Pd(OAc)_2$	PCy_3	Na_2CO_3	4A MS	DMF	31
11	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	4A MS	DMF	79
12	$Pd(OAc)_2$	PCy_3	K_3PO_4	4A MS	DMF	60
13	$Pd(OAc)_2$	PCy_3	Na_2OtBu	4A MS	DMF	44
14	$Pd(OAc)_2$	PCy_3	DBU	4A MS	DMF	trace
15	**$PdCl_2$**	**PCy_3**	**Cs_2CO_3**	**4A MS**	**DMF**	**87**
16	$Pd_2(dba)_3$	PCy_3	Cs_2CO_3	4A MS	DMF	52
17	$PdCl_2$	PPh3	Cs_2CO_3	4A MS	DMF	79
18	$PdCl_2$	(*R*)-BINAP	Cs_2CO_3	4A MS	DMF	22
19	$PdCl_2$	$BuPAd_2$	Cs_2CO_3	4A MS	DMF	53
20	$PdCl_2$	DPPP	Cs_2CO_3	4A MS	DMF	17
21	$PdCl_2$	DPEphos	Cs_2CO_3	4A MS	DMF	39

[a]Reaction conditions: All reactions were performed under argon with **1a** (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol), and additive (100 mg) in 2 mL of solvent at 135 °C for 18 h in a sealed tube. [b]Isolated yield. [c]Under N_2 at 120 °C for 12 h. [d]Under N_2 at 120 °C for 18 h. [e]120 °C. [f]100 °C.

triazoles, aminopyrroles, diimines, and dicarbonyl (Scheme 2) but also provide a rapid and valid access to build the construction of nitrogen heterocycles in cycloadditions.[14] Moreover, the α-iminonitriles are quite stable to high temperature (greater than 100 °C) and water, which make them an effective substitute for acylnitriles to participate in metal-catalyzed C−CN activation.[15] In addition to its widespread use in organic transformation, α-iminonitriles also exhibit diverse biological activities, such as inhibit the function of histamine-induced or acetylcholine-induced contraction in rat ileum.[16] As a result, many methodologies have been reported for the synthesis of α-iminonitriles.[7a,13a,17] However, most of them are multistep reactions, using complex substrates, excess oxidants, and various toxic cyanides such as Bu_3SnCN, $Hg(CN)_2$, NaCN, CuCN, and so on. Herein, we provide a new protocol for the synthesis of α-iminonitrile via palladium-

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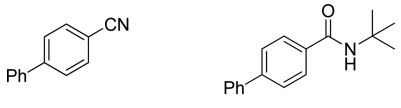
catalyzed double isocyanide insertion in one pot (Scheme 1e); of note is that the protocol employs no hypertoxic cyanides.

RESULTS AND DISCUSSION

An investigation was performed using 4-iodobiphenyl **1a** and *tert*-butyl isocyanide in the presence of $Pd(OAc)_2$ and PCy_3 with K_2CO_3 as a base, when the reaction was carried out in the solvent of dimethyl sulfoxide (DMSO) under nitrogen at 120 °C for 12 h, the desired product **2a** was found in 31% yield (Table 1, entry 1), along with minor amounts of **2aa** and **2ab** (Scheme 3); however, almost half of **1a** remained. A prolonged reaction time increased the yield to 44% (Table 1, entry 2).

Scheme 3. Byproducts in the Synthetic Reaction of 2a



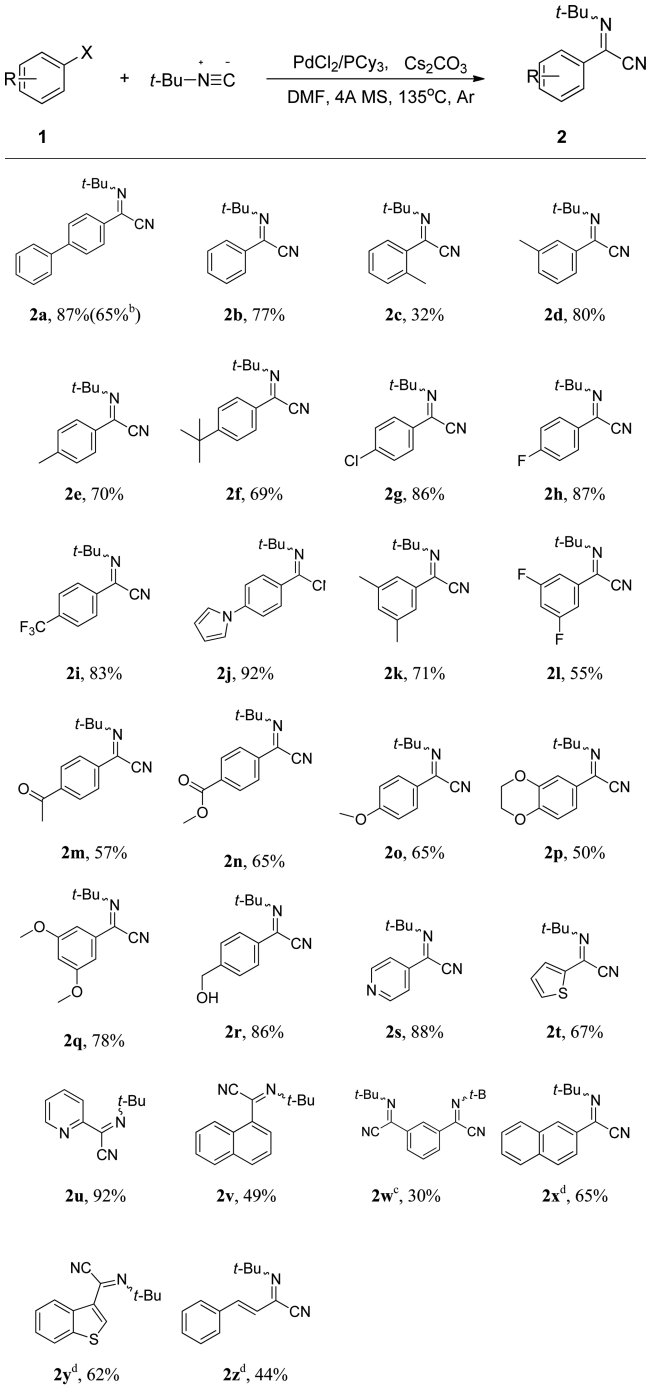
2aa **2ab**

Considering that water resulted in the formation of **2ab**, we used molecular sieves (4A MS) as an additive under argon; the yield was up to 57% (Table 1, entry 3). Raising the temperature led to an increase in the yield (Table 1, entries 3–5). Solvent screening showed that *N,N*-dimethylformamide (DMF) was optimal (Table 1, entries 5–8). Then, several bases were tested; with decreasing base strength, the yield of byproduct **2aa** increased. When the base was switched to Cs_2CO_3, to our surprise, the yield improved to 79% (Table 1, entry 11). Subsequently, other palladium sources also were investigated; however, none of them were superior to $PdCl_2$ (Table 1, entries 15–16). Phosphines played a pivotal role in the reaction. We conducted the reaction using other mono- or diphosphines and observed a better yield when using monophosphines compared to diphosphines; a higher yield was obtained when using PCy_3 (Table 1, entries 17–21). Eventually, the optimized reaction conditions included $PdCl_2$ (10 mol %) and PCy_3 (20 mol %) as the catalyst system, with Cs_2CO_3 (2 equiv) as the base, DMF as the solvent, and 4A MS as the additive under argon at 135 °C.

With the optimized conditions in hand, the substrate scope and limitations of this methodology were explored. As illustrated in Table 2, aryl iodides with electron-rich and -poor substituents (**2d–2f**, **2k**, **2o–2q**, **2g–2j**, **2l**), aryl bromides (**2x–2y**), and *α,β*-unsaturated aryl bromide (**2z**) were all compatible with the method, affording the respective products in moderate to excellent yields; also, electron-poor phenyl halides afforded higher yields than their electron-rich counterparts. 2-Methyliodobenzene gave product only in 33% yield (**2c**), which resulted from the steric hindrance in the *ortho*-position. In addition, the method tolerates a variety of functional groups, such as halogen, ketone (**2m**), ester (**2n**), and ether (**2o**, **2q**), also leading to the corresponding products in good yields. Unfortunately, several sensitive groups such as a phenolic hydroxy and aromatic amino were incompatible. Interestingly, 4-iodophenylmethanol (**2r**) could be converted into the corresponding *α*-iminonitrile in 86% yield. In addition, heteroaryl halides (**2s–2u, 2y**) also gave good results under the standard conditions. Meanwhile, the 1,3-diiodobenzene was converted into *N,N′*-di-*tert*-butylisophthalimidoyl cyanide in 31% yield (**2w**).

To extend the application of this reaction, various substituted isocyanides such as cyclohexyl (**3a**), phenylethyl (**3b**), 1-adamantyl (**3c**), 1,1,3,3-tetramethylbutyl (**3d**) isocyanides were investigated. Unfortunately, only the 1,1,3,3-tetramethylbutyl isocyanide could smoothly be transformed, giving *N*-(2,4,4-trimethylpentan-2-yl)-[1,1′-biphenyl]-4-carbimidoyl cyanide (**3d**) in 71% yield (Scheme 4). The results suggested the

Table 2. Palladium-Catalyzed Synthesis of *α*-Iminonitriles[a]



[a]All reactions were performed under argon with aryl iodides (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), catalyst (0.05 mmol), ligand (0.1 mmol), base (1 mmol), and additive (100 mg) in 2 mL of solvent at 135 °C for 18 h in a sealed tube; isolated yields. [b]Using 4-bromobiphenyl instead of 4-iodobiphenyl. [c]Aryl halides (0.5 mmol), *tert*-butyl isocyanide (3 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), and additive (100 mg) in 2 mL of solvent. [d]Aryl bromides.

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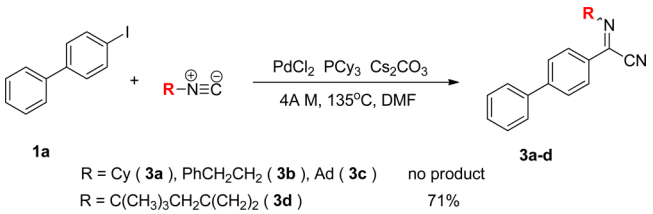
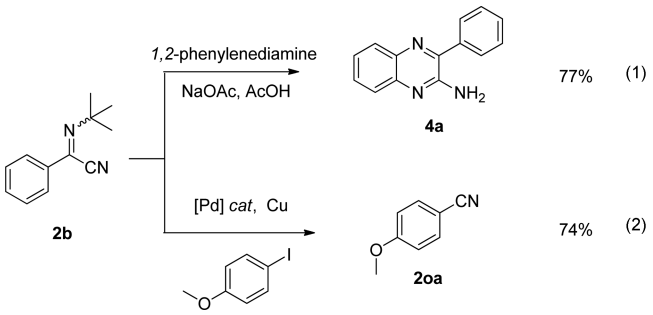
Scheme 4. Scope of Isocyanide Double Insertion



importance of the quaternary carbon. In addition, the steric hindrance of isocyanides with different substituents has a large influence on this kind of reaction, and we consider that **3d** and *tert*-butyl isocyanide are more prone to eliminate to transform into cyano.

Next, to further explore the synthetic utility of our methodology, we performed a number of preliminary experiments as depicted in Scheme 5. When **2** was refluxed under

Scheme 5. Transformation of 2



acetic acid with 1,2-phenylenediamine in the presence of NaOAc, 3-phenylquinoxalin-2-amine (**4a**) was formed in 77% yield (Scheme 5, eq 1). Also, a benzonitrilic compound (**2oa**) was formed in 74% yield (Scheme 5, eq 2) with dissolving iodobenzene and **2** in DMSO in the presence of $Pd(OAc)_2$ and $Cu(TFA)_2$ at 120 °C, which showed that **2** could be used as a cyano source; further studies are underway in our laboratory. The compounds of **4a** are common building blocks found in many biologically and pharmaceutically active compounds,[18] and the compounds of **2oa** are important intermediates in organic synthesis.[19]

On the basis of literature reports,[3c,6,10] a plausible mechanism for this reaction is depicted in Scheme 6. First, oxidative addition of **1** to the Pd(0) catalyst leads to the palladium complex **A**, followed by *tert*-butyl isocyanide insertion to form intermediate **B**. Subsequently, the second isocyanide insertion takes place to form intermediate **C**. With the assistance of Cs_2CO_3, intermediate **C** undergoes *tert*-butyl elimination and Pd expulsion to form the product **2**.

CONCLUSION

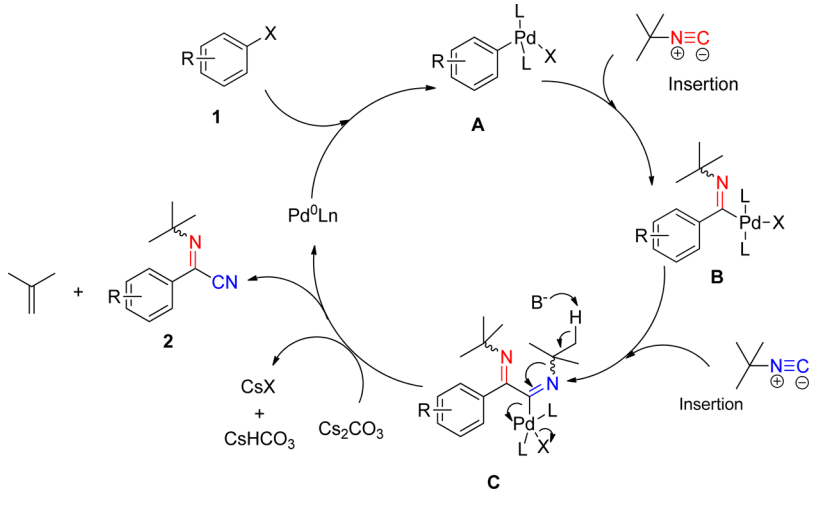
In summary, we have illustrated a simple and efficient approach for palladium-catalyzed synthesis of α-iminonitrile *via* *tert*-butyl isocyanide double insertion and elimination in one pot. In this reaction, we overcame the challenge of isocyanide polymerization in the presence of a transition metal in a double isocyanide insertion, achieving isocyanides as a cyano source without any oxidants. Compared to others methods, the reaction is tolerant of a wide range of substrates and is more efficient, convenient, and less toxic for the synthesis of α-iminonitrile.

EXPERIMENTAL SECTION

General Information. Reactants and reagents were purchased from commercial suppliers. All solvents were dried and freshly distilled. TLC was performed on silica HSGF254 plates. Melting points were determined with a digital melting-point apparatus. NMR spectra were run in a solution of deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) as the internal standard and were reported in parts per million (ppm). ^1H and ^{13}C NMR spectra were obtained at 400/101 MHz ($^1H/^{13}C$), respectively. High-resolution mass spectra (HRMS) analyses were carried out on a chemical ionization (CI) apparatus using time-of-flight (TOF) mass spectrometry. Infrared (IR) data were obtained using KBr tablets, and wavenumbers are reported in cm^{-1}.

General Procedure for the Synthesis of α-Iminonitrile. 1 (0.5 mmol), *tert*-butyl isocyanide (1.5 mmol), $PdCl_2$ (0.05 mmol), PCy_3 (0.1 mmol), Cs_2CO_3 (1.0 mmol), and 4A MS (100 mg) were added into a 15 mL sealed tube equipped with a magnetic stirring bar. The mixture was stirred in DMF (2 mL) under argon at 135 °C for 18 h. After completion of the reaction as indicated by TLC, it was poured into water (30 mL) and extracted by ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

Scheme 6. Plausible Reaction Mechanism



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Preparation of 3-Phenylquinoxalin-2-amine (4a). To a solution of **2** (0.4 mmol), 1,2-phenylenediamine (0.6 mmol) and NaOAc (1 mmol) in AcOH (4 mL) were added in a round-bottom flask. The reaction mixture was refluxed for 2 h. After the mixture cooled to room temperature, it was concentrated in vacuo, then washed with brine, and extracted with DCM (10 mL × 3). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

Preparation of 4-Methoxybenzonitrile (2oa). 1-Iodo-4-methoxybenzene (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.05 mmol), and $Cu(TFA)_2$ (0.6 mmol) were added into a 15 mL sealed tube equipped with a magnetic stirring bar. The mixture was stirred in DMSO (1.5 mL) at 120 °C for 10 h. After completion of the reaction as indicated by TLC, the mixture was poured into water (30 mL) and extracted by ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using petroleum ether/EtOAc as the eluent to give the pure target product.

*N-(tert-Butyl)-[1,1′-biphenyl]-4-carbimidoyl Cyanide (**2a**).* White solid (114 mg, 87% yield). Mp: 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 7.9 Hz, 2H), 7.66 (d, J = 7.9 Hz, 2H), 7.61 (d, J = 7.4 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H), 7.38 (t, J = 7.1 Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6 (s), 140.0 (s), 134.3 (s), 129.1 (s), 128.2 (s), 127.7 (s), 127.4 (s), 127.3 (s), 111.9 (s), 58.6 (s), 29.5 (s). IR (KBr): ν 2971, 2918, 2213, 1669, 1592, 1475, 1363, 1205, 1181, 999, 843 cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{19}N_2$ [M + H]$^+$, 263.1548; found, 263.1555.

*N-(tert-Butyl)-benzimidoyl Cyanide (**2b**).*[17a] Yellow oil (72 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.4 Hz, 2H), 7.53−7.41 (m, 3H), 1.54 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 136.8 (s), 131.8 (s), 128.8 (s), 127.3 (s), 111.8 (s), 58.5 (s), 29.5 (s). HRMS (CI): m/z calcd for $C_{12}H_{14}N_2$ [M + H]$^+$, 186.1157; found, 186.1154.

*N-(tert-Butyl)-2-methylbenzimidoyl Cyanide (**2c**).* Colorless oil (32 mg, 32% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.37−7.27 (m, 2H), 7.24 (d, J = 7.6 Hz, 1H), 2.49 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8 (s), 137.2 (s), 135.4 (s), 131.9(s), 130.5 (s), 129.3 (s), 126.4 (s), 112.6(s), 59.2 (s), 29.5 (s), 21.0 (s). IR (KBr): ν 2970, 2926, 2856, 2212, 1676, 1615, 1457, 1363, 1202, 990, 878, 756, 722 cm^{-1}. HRMS (CI): m/z calcd for $C_{13}H_{17}N_2$ [M + H]$^+$, 201.1392; found, 201.1385.

*N-(tert-Butyl)-3-methylbenzimidoyl Cyanide (**2d**).* Yellow oil (80 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 6.8 Hz, 2H), 7.34 (q, J = 7.7 Hz, 2H), 2.42 (s, 3H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7 (s), 137.0 (s), 135.3 (s), 132.6 (s), 128.7 (s), 127.6 (s), 124.6 (s), 111.9 (s), 58.4 (s), 29.4 (s), 21.5 (s). IR (KBr): ν 2972, 2929, 2872, 2216, 1603, 1585, 1460, 1304, 1206, 1020, 790, 700 cm^{-1}. HRMS (CI): m/z calcd for $C_{13}H_{17}N_2$ [M + H]$^+$, 201.1392; found, 201.1395.

*N-(tert-Butyl)-4-methylbenzimidoyl Cyanide (**2e**).*[17a] Colorless oil (70 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 2.40 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4 (s), 136.7 (s), 132.9 (s), 129.5 (s), 127.2 (s), 112.0 (s), 58.3 (s), 29.5 (s), 21.6 (s). HRMS (CI): m/z calcd for $C_{13}H_{17}N_2$ [M + H]$^+$, 201.1392; found, 201.1389.

*N,4-Di-tert-butylbenzimidoyl Cyanide (**2f**).* White solid (83 mg, 69% yield) Mp: 47−48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 8.5 Hz, 2H), 1.54 (s, 9H), 1.36 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5 (s), 136.6 (s), 132.8 (s), 127.1 (s), 125.8 (s), 111.9 (s), 58.3 (s), 35.1 (s), 31.2 (s), 29.5 (s). IR (KBr): ν 2965, 2926, 2869, 2211, 1612, 1595, 1462, 1362, 1266, 1204, 999, 837, 657 cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{23}N_2$ [M + H]$^+$, 243.1861; found, 243.1835.

*N-(tert-Butyl)-4-chlorobenzimidoyl Cyanide (**2g**).*[17c] Yellow oil (95 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2 (s), 135.7 (s), 133.8 (s), 129.1 (s), 128.5 (s), 111.5 (s), 58.7 (s), 29.4 (s). HRMS (CI): m/z calcd for $C_{12}H_{14}N_2Cl$ [M + H]$^+$, 221.0846; found, 221.0851.

*N-(tert-Butyl)-4-fluorobenzimidoyl Cyanide (**2h**).* Yellow oil (90 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (ddd, J = 8.8, 5.3, 1.6 Hz, 2H), 7.17−7.10 (m, 2H), 1.52 (d, J = 1.6 Hz, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (s), 163.9 (s), 135.5 (s), 131.7 (d, J = 3.1 Hz), 129.5 (d, J = 8.9 Hz), 116.1 (s), 115.9 (s), 111.7 (s), 58.6 (s), 29.5 (s). IR (KBr): ν 2972, 2927, 2855, 2215, 1614, 1601, 1588, 1507, 1230, 1156, 842 cm^{-1}. HRMS (CI): m/z calcd for $C_{12}H_{14}N_2F$ [M + H]$^+$, 205.1141; found, 205.1133.

*N-(tert-Butyl)-4-(trifluoromethyl)benzimidoyl Cyanide (**2i**).* White solid (105 mg, 83% yield). Mp: 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.2 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 1.55 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.28 (s), 135.64 (s), 133.98 (s), 133.65 (s), 133.33 (s), 133.00 (s), 127.69 (s), 125.85 (t, J = 5.7 Hz), 125.18 (s), 122.47 (s), 119.77 (s), 111.43 (s), 59.22 (s), 29.42 (s). IR (KBr): ν 2972, 2927, 2855, 2216, 1639, 1618, 1460, 1324, 1164, 1126, 1013 cm^{-1}. HRMS (CI): m/z calcd for $C_{13}H_{14}N_2F_3$ [M + H]$^+$, 255.1109; found, 255.1120.

*N-(tert-Butyl)-4-(1H-pyrrol-1-yl)benzimidoyl Cyanide (**2j**).* White solid (115 mg, 92% yield). Mp: 77−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 7.19−7.16 (m, 2H), 6.42−6.39 (m, 2H), 1.56 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2 (s), 135.8 (s), 132.4 (s), 128.8 (s), 119.8 (s), 119.1 (s), 111.7 (s), 111.5 (s), 58.6 (s), 29.5 (s). IR (KBr): ν 2967, 2919, 2850, 2226, 1669, 1604, 1519, 1477, 1334, 1183, 1066, 842, 723 cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{18}N_3$ [M + H]$^+$, 252.1501; found, 252.1497.

*N-(tert-Butyl)-3,5-dimethylbenzimidoyl Cyanide (**2k**).* Yellow oil (76 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 2H), 7.13 (s, 1H), 2.37 (s, 6H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6 (s), 137.2 (s), 135.4 (s), 133.6 (s), 125.0 (s), 112.0 (s), 58.4 (s), 29.5 (s), 21.3 (s). IR (KBr): ν 2996, 2970, 2922, 2869, 2214, 1601, 1588, 1457, 1363, 1183, 1160, 856, 704 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{19}N_2$ [M + H]$^+$, 215.1548; found, 215.1542.

*N-(tert-Butyl)-3,5-difluorobenzimidoyl Cyanide (**2l**).* Yellow oil (61 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.4 Hz, 2H), 6.96 (d, J = 7.3 Hz, 1H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47 (d, J = 12.3 Hz), 161.99 (d, J = 12.3 Hz), 138.51 (t, J = 9.2 Hz), 134.66 (t, J = 4.0 Hz), 111.16 (s), 110.63−110.15 (m), 107.44 (s), 107.19 (s), 106.93 (s), 59.24 (s), 29.39 (s). IR (KBr): ν 2955, 2921, 2852, 2215, 1620, 1594, 1460, 1329, 1123, 992 cm^{-1}. HRMS (CI): m/z calcd for $C_{12}H_{13}N_2F_2$ [M + H]$^+$, 223.1047; found, 223.1035.

*4-Acetyl-N-(tert-butyl)benzimidoyl Cyanide (**2m**).* Yellow solid (65 mg, 57% yield). Mp: 87−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 2H), 2.63 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.5 (s), 139.3 (s), 138.9 (s), 136.0 (s), 128.7 (s), 127.5 (s), 111.5 (s), 59.1 (s), 29.4 (s), 27.0 (s). IR (KBr): ν 2972, 2917, 2850, 2600, 2218, 1685, 1607, 1592, 1420, 1366, 1260, 1204, 1005, 954, 851, 835, 671 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{17}N_2O$ [M + H]$^+$, 229.1341; found, 229.1335.

*Methyl 4-((tert-Butylimino)(cyano)methyl)benzoate (**2n**).* Yellow solid (79 mg, 65% yield). Mp: 79−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.5 Hz, 2H), 8.04 (d, J = 8.3 Hz, 2H), 3.94 (s, 3H), 1.53 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4 (s), 138.9 (s), 136.1 (s), 132.9 (s), 130.0 (s), 127.3 (s), 111.5 (s), 59.1 (s), 52.5 (s), 29.4 (s). IR (KBr): ν 3067, 2994, 2971, 2949, 2219, 1719, 1613, 1593, 1265, 1204, 1106, 871, 776, 700 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{17}N_2O_2$ [M + H]$^+$, 245.1290; found, 245.1287.

*N-(tert-Butyl)-4-methoxybenzimidoyl Cyanide (**2o**).*[17a] Yellow oil (70 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 1.52 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (s), 136.1 (s), 128.9 (s), 128.4 (s), 114.1 (s), 111.9 (s), 58.0 (s), 55.5 (s), 29.5 (s). HRMS (CI): m/z calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$, 217.1341; found, 217.1338.

*N-(tert-Butyl)-2,3-dihydrobenzo[b][1,4]dioxine-6-carbimidoyl Cyanide (**2p**).* Yellow oil (61 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 2.1 Hz, 1H), 7.48 (dd, J = 8.5, 2.1 Hz, 1H), 6.91 (d, J = 8.5 Hz, 1H), 4.29 (d, J = 5.1 Hz, 2H), 4.27 (d, J = 5.1 Hz, 2H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0 (s), 143.8 (s), 135.8 (s), 129.2 (s), 121.0 (s), 117.5 (s), 116.1 (s), 111.8 (s), 64.7 (s),

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J. Org. Chem. 2016, 81, 1610−1616

64.3 (s), 58.1 (s), 29.5 (s). IR (KBr): ν 2969, 2932, 2877, 2216, 1666, 1579, 1504, 1291, 1065, 889 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{17}N_2O_2$ [M + H]$^+$, 245.1290; found, 245.1293.

*N-(tert-Butyl)-3,5-dimethoxybenzimidoyl Cyanide (**2q**).* White solid (96 mg, 78% yield). Mp: 99−101 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 2.0 Hz, 2H), 6.59 (s, 1H), 3.84 (s, 6H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1 (s), 137.4 (s), 136.7 (s), 111.8 (s), 105.2 (s), 104.3 (s), 58.6 (s), 55.7 (s), 29.5 (s). IR (KBr): ν 2976, 2939, 2833, 2212, 1606, 1586, 1458, 1308, 1207, 1154, 1066, 1021 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{19}N_2O_2$ [M + H]$^+$, 247.1447; found, 247.1452.

*N-(tert-Butyl)-4-(hydroxymethyl)benzimidoyl Cyanide (**2r**).* Yellow oil (93 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 4.75 (s, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.9 (s), 136.5 (s), 134.7 (s), 127.5 (s), 127.0 (s), 111.9 (s), 64.8 (s), 58.6 (s), 29.5 (s). IR (KBr): ν 3348, 2971, 2932, 2858, 2214, 1721, 1594, 1572, 1364, 1264, 1203, 1004, 825, 676 cm^{-1}. HRMS (CI): m/z calcd for $C_{13}H_{17}N_2O$ [M + H]$^+$, 217.1341; found, 217.1342.

*N-(tert-Butyl)isonicotinimidoyl Cyanide (**2s**).* Yellow oil (82 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 4.5 Hz, 2H), 7.82 (d, J = 4.5 Hz, 2H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7 (s), 142.0(s), 135.4 (s), 120.8 (s), 111.0 (s), 59.6 (s), 29.4 (s). IR (KBr): ν 2966, 2928, 2853, 2215, 1703, 1614, 1593, 1408, 1364, 1278, 1218, 1188, 1008, 988 cm^{-1}. HRMS (CI): m/z calcd for $C_{11}H_{14}N_3$ [M + H]$^+$, 188.1188; found,188.1184.

*N-(tert-Butyl)thiophene-2-carbimidoyl Cyanide (**2t**).* Yellow oil (64 mg, 67% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.61 (m, 1H), 7.45 (d, J = 5.6 Hz, 1H), 7.12−7.09 (m, 1H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1 (s), 130.9 (d, J = 11.3 Hz), 127.9 (s), 111.3 (s), 58.5 (s), 29.6 (s). IR (KBr): ν 2971, 2925, 2854, 2218, 1654, 1597, 1580, 1425, 1364, 1203, 955, 850, 711 cm^{-1}. HRMS (CI): m/z calcd for $C_{10}H_{13}N_2S$ [M + H]$^+$, 193.0799; found, 193.0787.

*N-(tert-Butyl)picolinimidoyl Cyanide (**2u**).* Yellow solid (99 mg, 92% yield). Mp: 35−37 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 5.6 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.75 (t, J = 8.3 Hz, 1H), 7.41−7.36 (m, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2 (s), 149.4 (s), 138.4 (s), 136.9 (s), 125.8 (s), 121.0 (s), 111.8 (s), 58.9 (s), 29.3 (s). IR (KBr): ν 2971, 2924, 2853, 2220, 1620, 1604, 1583, 1464, 1364, 1207, 1012, 793, 742 cm^{-1}. HRMS (CI): m/z calcd for $C_{11}H_{14}N_3$ [M + H]$^+$, 188.1188; found, 188.1176.

*N-(tert-Butyl)-1-naphthimidoyl Cyanide (**2v**).* Yellow oil (58 mg, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.4 Hz, 1H), 7.98−7.89 (m, 3H), 7.62−7.53 (m, 3H), 1.66 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7 (s), 134.2 (s), 132.6 (s), 132.0 (s), 130.2 (s), 128.9 (d, J = 8.5 Hz), 127.9 (s), 126.7 (s), 124.9 (d, J = 2.7 Hz), 112.9 (s), 59.5 (s), 29.6 (s). IR (KBr): ν 2970, 2927, 2854, 2222, 1611, 1590, 1510, 1364, 1202, 954, 801, 772 cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{17}N_2$ [M + H]$^+$, 237.1392; found, 237.1388.

*N,N′-Di-tert-butylisophthalimidoyl Cyanide (**2w**).* Colorless oil (43 mg, 30% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.39 (dd, J = 7.8, 1.7 Hz, 2H), 7.83 (t, J = 7.8 Hz, 1H), 1.83 (s, 18H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.0 (d, J = 4.7 Hz), 130.3 (s), 129.3 (s), 125.8 (s), 111.5 (s), 59.0 (s), 29.4 (s). IR (KBr): ν 2972, 2926, 2854, 2217, 1607, 1582, 1462, 1365, 1190, 1031, 806, 690 cm^{-1}. HRMS (CI): m/z calcd for $C_{18}H_{23}N_4$ [M + H]$^+$, 295.1923; found, 295.1919.

*N-(tert-Butyl)-2-naphthimidoyl Cyanide (**2x**).* White solid (77 mg, 65% yield). Mp: 50−53 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.13 (d, J = 8.7 Hz, 1H), 7.97 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.3 Hz, 2H), 7.60−7.54 (m, 2H), 1.60 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.9 (s), 135.1 (s), 133.0 (s), 132.9 (s), 129.3 (s), 129.2 (s), 128.7 (s), 128.1 (s), 127.9 (s), 127.0 (s), 122.8 (s), 111.9 (s), 58.6 (s), 29.6 (s). IR (KBr): ν 2972, 2921, 2851, 2215, 1596, 1459, 1361, 1277, 1187, 1124, 862, 820, 751 cm^{-1}. HRMS (CI): m/z calcd for $C_{16}H_{17}N_2$ [M + H]$^+$, 237.1392; found, 237.1386.

*N-(tert-Butyl)-3a,7a-dihydrobenzo[b]thiophene-3-carbimidoyl Cyanide (**2y**).* White solid (75 mg, 62% yield). Mp: 76−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.50−7.42 (m, 2H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0 (s), 135.7 (s), 134.8 (s), 132.9 (s), 132.7 (s), 126.0 (s), 125.9 (s), 125.7 (s), 122.6 (s), 111.9 (s), 58.6 (s), 29.6 (s). IR (KBr): ν 2984, 2971, 2919, 2845, 2219, 1614, 1587, 1460, 1361, 1189, 892, 769 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{15}N_2S$ [M + H]$^+$, 243.0956; found, 243.0961.

*N-(tert-Butyl)cinnamimidoyl Cyanide (**2z**).* Yellow oil (47 mg, 44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (dd, J = 7.5, 1.6 Hz, 2H), 7.40 (t, J = 11.9 Hz, 4H), 6.93 (d, J = 16.4 Hz, 1H), 1.49 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1 (s), 138.2 (s), 134.9 (s), 130.1 (s), 129.1 (s), 128.5 (s), 127.9 (s), 111.2 (s), 58.6 (s), 29.6 (s). IR (KBr): ν 2970, 2927, 2855, 2218, 1704, 1626, 1580, 1449, 1364, 1192, 966, 753, 691 cm^{-1}. HRMS (CI): m/z calcd for $C_{14}H_{17}N_2$ [M + H]$^+$, 213.1392; found, 213.1396.

*N-(2,4,4-Trimethylpentan-2-yl)-[1,1′-biphenyl]-4-carbimidoyl Cyanide (**3d**).* Colorless oil (113 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 2H), 7.67 (dd, J = 23.1, 8.1 Hz, 4H), 7.45 (dt, J = 14.6, 7.8 Hz, 3H), 1.94 (s, 2H), 1.62 (s, 6H), 1.04 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4 (s), 140.1 (s), 135.2 (s), 134.6 (s), 129.1 (s), 128.2 (s), 127.8 (s), 127.4 (d, J = 19.7 Hz), 112.2 (s), 62.5 (s), 56.6 (s), 32.0 (s), 29.6 (s). IR (KBr): ν 2952, 2869, 2212, 1596, 1485, 1365, 1214, 1003, 846, 766, 729, 695 cm^{-1}. HRMS (CI): m/z calcd for $C_{22}H_{27}N_2$ [M + H]$^+$, 319.2174; found, 319.2169.

*3-Phenylquinoxalin-2-amine (**4a**).*[18e] Yellow solid (68 mg, 77% yield). Mp: 181−183 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.78 (d, J = 6.8 Hz, 2H), 7.70 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.45 (t, J = 7.0 Hz, 2H), 5.17 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6 (s), 146.0 (s), 141.3 (s), 138.2 (s), 137.1 (s), 130.2 (s), 129.9 (s), 129.4 (s), 129.2 (s), 128.5 (s), 125.7 (s), 125.5 (s). HRMS (CI): m/z calcd for $C_{14}H_{12}N_3$ [M + H]$^+$, 222.1031; found, 222.1035.

*4-Methoxy-benzonitrile (**2oa**).*[6d] White solid (29 mg, 74% yield). Mp: 62−63 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 5.1 Hz, 1H), 6.93 (d, J = 5.2 Hz, 1H), 3.83 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9 (s), 134.0 (s), 119.2 (s), 114.8 (s), 103.9 (s), 55.6 (s). HRMS (CI): m/z calcd for C_8H_8NO [M + H]$^+$, 134.0606; found, 134.0604.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02777.

Figures giving ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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